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Synthesis and application of a new pseudo C_2-symmetric tertiary diamine for the enantioselective addition of MeLi to aromatic imines

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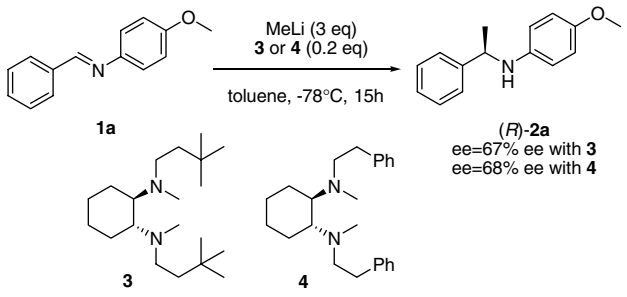
Abstract—A new tertiary pseudo C_2-symmetric diamine derived from (1*S*,2*S*)-(+)-pseudoephedrine was synthesized and tested in the enantioselective addition of methyllithium on different aromatic imines. A comparative study with a similar C_2-symmetric ligand derived from the cyclohexane diamine showed better reactivity and enantioselectivity up to 91%.

1. Introduction

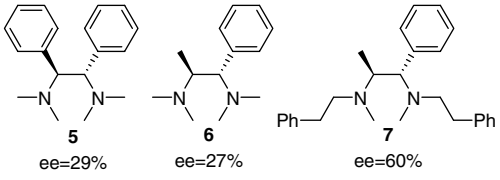
Many ligands in asymmetric catalysis are C_2-symmetric to reduce the number of possible transition states and consequently the number of possible diastereoisomers.

In our previous article, we developed a new type of C_2-symmetric tertiary diamine derived from a cyclohexane diamine backbone for the addition of alkyllithium or aryllithium to aromatic imines.[1] We showed that the nitrogen atom, complexed with a metal, such as lithium, could become a stereogenic center in the reactive reagent due to a chirality transfer from the chiral backbone. A large number of ligands based on the cyclohexane diamine backbone were tested and two of them **3** and **4** appeared to be the best (Scheme 1).



Scheme 1.

After such promising results, it was reasonable to believe that the cyclohexane core could be replaced by another chiral backbone (more flexible), to optimize this enantioselective addition of methyllithium. Ligands **5** and **6** (Scheme 2) were tested in the same reaction described in Scheme 1.[2]



Scheme 2.

Their selectivity was almost the same[3] but **5** is much more difficult to synthesize compared to **6** prepared from the commercial enantiomerically pure (1*S*,2*S*)-(+)-pseudoephedrine. This represents an interesting feature given that pseudoephedrine derivatives could be easily prepared enantiomerically pure and with the same selectivity than the analogous (1*S*-2*S*)-diphenyldiaminoethane. By analogy with **3** and **4**, ligand **7** was the first to be synthesized and tested. It showed better reactivity but lower selectivity than its analogue **4**.[4] In continuity of this work, we decided to synthesize the analogue of **3** starting from (1*S*,2*S*)-(+)-pseudoephedrine, which is commercially available. In addition, it was shown that a strong base, such as *n*-BuLi, could

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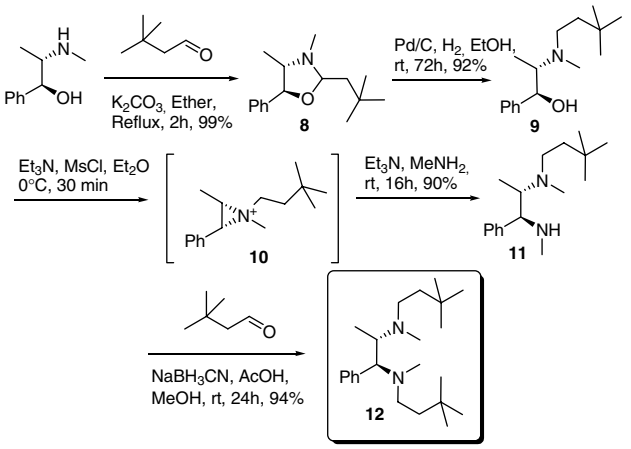
deprotonate **4** and **7** and release styrene, even at −78 °C.[5] This would not be the case with **3** and its analogues.

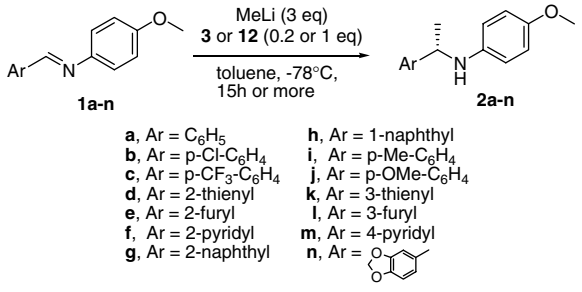
2. Results and discussion

Diamine **12** was synthesized in a four step sequence starting from (1*S*,2*S*)-(+)-pseudoephedrine in 77% overall yield (Scheme 3).



Scheme 3.

Oxazolidine **8** was the result of the condensation of 3,3-dimethylbutyraldehyde with (1*S*,2*S*)-(+)-pseudoephedrine.[6] Amino-alcohol **9** was then obtained after reduction of oxazolidine **8** with palladium on charcoal (0.01 equiv) under 1 atm of H_2.[7] Other reducing agents, such as $NaBH_4$, $NaBH_3CN$, or $LiAlH_4$ were tried but without any success. Reacting **9** under basic conditions with methanesulfonyl chloride gave an aziridinium intermediate salt **10**.[8] The latter was opened regiospecifically by a commercial methylamine solution in ethanol, to afford **11** in quantitative yield with an overall retention of the configuration.[9] Finally, ligand **12** was obtained in quantitative yield after reductive amination of **11** with sodium cyanoborohydride activated by acetic acid in methanol.[10] Diamine **12** was then tested in the enantioselective addition of MeLi to various *N*-*p*-methoxyphenyl imines (Scheme 4). The same reaction conditions as previously reported[1] were applied for the purpose of comparison with diamines **3**.



Scheme 4.

As far as **12** is concerned, in almost all cases, very good conversion occurred and isolated yields were very similar to **3**. Nevertheless, it is interesting to note that for **1b** the reaction was performed at −65 °C due to low reactivity at −78 °C with **3**, but carrying out the reaction with **12** allowed us to stay at −78 °C and still obtain complete conversion (entry 3 vs entry 4). Systematic inversion of configuration was obtained for all products, as expected with the inversion of configuration at the chiral backbone of the diamines. In terms of selectivity, in all cases, diamine **12** induced better enantioselectivity than **3**. The bigger difference appeared for imine **1a** (entry 1 vs entry 2). For imines **1d–f** we observed an increase of reactivity but a decrease in term of selectivity (entries 8, 10, and 12). In fact, in these cases, the substrate itself behaves like a ligand in chelating the MeLi. This is why the stronger the chelation, the better the conversion is, but the less the selectivity is induced, due to the achirality of the substrate. To avoid such behavior, we changed the substrate **1d–f** by their position isomers **1k–m** where the chelation is not possible.

Table 1. Enantioselective addition of MeLi to imines **1a–n** promoted by diamines **3** or **12**

Entry	Product	Lig (equiv)	Conv[a] (%)	ee[b,c] (%)
1	**2a**	**3**[g] (0.2)	— (98)	67 (*R*)
2	**2a**	**12** (0.2)	100 (72)	88 (*S*)
3	**2b**[d]	**3** (0.2)	— (70)	57 (*R*)
4	**2b**	**12** (0.2)	100 (75)	69 (*S*)
5	**2c**	**3** (0.2)	— (70)	38 (*R*)
6	**2c**	**12** (0.2)	90 (81)	57 (*S*)
7	**2d**	**3** (0.2)	— (93)	58 (*R*)
8	**2d**	**12** (0.2)	80 (76)	66 (*S*)
9	**2e**	**3** (0.2)	— (94)	20 (*R*)
10	**2e**	**12** (0.2)	96 (83)	19 (*S*)
11	**2f**	**3** (0.2)	— (87)	4 (*R*)
12	**2f**	**12** (0.2)	100 (77)	3 (*S*)
13	**2g**[e]	**3** (0.2)	— (78)	42 (*R*)
14	**2g**[e]	**12** (0.2)	100 (97)	45 (*S*)
15	**2g**	**12** (1)	100 (90)	79 (*S*)
16	**2h**	**12** (1)	100 (74)	76 (*S*)
17	**2i**	**12** (0.2)	99 (88)	82 (*S*)
18	**2j**[f]	**12** (1)	88 (85)	91 (*S*)
19	**2k**	**12** (1)	76 (53)	81 (*S*)
20	**2l**	**12** (1)	95 (90)	75 (*S*)
21	**2m**[f]	**12** (1)	90 (93)	62 (*S*)
22	**2n**	**12** (1)	93 (92)	88 (*S*)

[a] Determined by ^1H NMR spectroscopy of the crude. Yield of isolated product in parenthesis.
[b] Determined by supercritical fluid chromatography.
[c] The absolute configuration of **2a** was determined on the basis of previous work. For other products, the configurations were assigned by consideration of the stereochemical pathway and of the systematic inversion of configuration occurring using **3** or **12**.
[d] Reaction carried out at −65 °C.
[e] Reaction carried out at −30 °C.
[f] Reaction time: 38 h.
[g] Reactions with **3** see Ref. 1.

To further optimize the reaction conditions, we first decided to increase the temperature to obtain complete conversion, but a dramatic decrease of selectivity was observed. As a result, we increased the catalyst amount to 1 equiv in case of incomplete reaction after 15 h. For **1a–c** and **1i**, the conditions were already optimized and

Table 2. Tests of catalyst loading on imine **1i** after 15 h

Entry	Diamine **12** (mol %)	Conv (%)	ee (%)
1	5	47	74
2	10	78	82
3	15	88	82
4	20	100	82

we obtain complete conversion with 20 mol % of **12**, which proved that this reaction, in term of conversion, is not very sensitive to electronic effects of the substituent on the aromatic part. However in terms of selectivity, substrates bearing electronic donor substituents induced more enantioselectivity contrary to those bearing an electron acceptor (entry 17 vs entry 6). For the other substrates, 1 equiv of catalyst was used and the time was extended to 38 h in case of partial conversion. Under such conditions, we managed to obtain almost complete conversion with naphthyl or heteroaromatic derivatives, and good selectivity up to 91% was observed (entries 15, 16, and 19–21). Catalyst loading (5, 10, and 15 mol %) has been also tested on the substrate **1i** under the same conditions as previously described (Scheme 4).

As expected, the conversion decreased with less catalyst, but the enantioselectivity was unaffected until 10 mol % of catalyst. We also wanted to compare this new catalyst with our previous one such as **3** or (−)-sparteine in the addition of *n*-BuLi on imine **1a**, in toluene at −78 °C during 2 h with 2 equiv of ligand.

With **3**, only 61% conversion occurred, whereas (−)-sparteine afforded 100%, and in both cases around 25% enantiomeric excess was measured. With **12**, the reaction was quantitative and we managed to obtain the (*S*)-enantiomer of **1a** in 50% enantiomeric excess (Tables 1–3).

Table 3. *n*-BuLi addition to imine **1a**

Entry	Diamine	Conv (%)	ee (%)
1	**3**	61	25
2	(−)-Sparteine	100	25
3	**12**	100	50

3. Conclusion

In conclusion, this new tertiary pseudo C_2-symmetric diamines **12** was easily synthesized in a four step sequence starting from the commercial enantiomerically pure (1*S*,2*S*)-(+)-pseudoephedrine. It was tested in the addition of MeLi on different aromatic imines **1a**–**n**, and with *n*-BuLi on **1a**. By comparison with the analogous C_2-symmetric cyclohexane diamines based **3**, and even with all the ligands previously described in our laboratory, better conversions and enantioselectivities were obtained in all cases with **12**. This study confirmed the potential of pseudo C_2-symmetric diamines based on the pseudoephedrine core and describes a general procedure for the synthesis of various other diamines.

Acknowledgments

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6. 2-(2,2-Dimethyl-propyl)-3,4-dimethyl-5-phenyl-oxazolidine **8** was prepared according to the procedure described in: Bergmann, E. D.; Zimkin, E.; Pinchas, S. *Rec. Trav. Chim. Pays-Bas.* **1952**, *71*, 237; 3-3-dimethylbutyraldehyde (80 μl, 0.605 mmol) and (1*S*,2*S*)-(+)-pseudoephedrine (100 mg, 0.605 mmol) were mixed in ether. Heat was evolved and an insoluble layer (mostly water) was formed. Potassium carbonate (85 mg, 0.605 mmol) was added and the whole mixture was refluxed for 2 h. After 2 h, TLC showed the reaction was over, the mixture was then filtered and the solvent evaporated under rotatory evaporator to yield 149 mg (100%) of **8** as a colorless oil. ^{1}H NMR ($CDCl_3$, δ = ppm, J = Hz): $\delta = 1.05$ (s, 9H), 1.2 (d, 3H, $J = 6$), 1.6 (dd, 1H, $J = 7.8$ and 14.4), 1.7 (d, 1H, $J = 14.9$), 2.3 (s and m, 4H), 4.2 (d, 1H, $J = 7.8$), 4.6 (d, 1H, $J = 8,6$), 7.2–7.5 (m, 5H).
7. 2-[(3,3-Dimethyl-butyl)-methyl-amino]-1-phenyl-propan-1-ol **9** was prepared according to the procedure described in: Gil-Av, E. *J. Am. Chem. Soc.* **1952**, *74*, 1346: A solution of (2,2-dimethyl-propyl)-3,4-dimethyl-5-phenyl-oxazolidine **8** (1.49 g, 6 mmol) in 13.5 ml of ethanol was hydrogenated with palladium on charcoal (0.01 equiv) at 35 °C under 1 atm of H_2 during 36 h. The mixture was filtered on Celite, then the solvents were removed to yield 1.37 g (91%) of **9** as a yellow oil; ^{1}H NMR ($CDCl_3$, δ = ppm, J = Hz): $\delta = 0.8$ (d, 3H, $J = 6.6$), 1 (s, 9H), 1.4–1.6 (m, 2H), 2.3 (s, 3H), 2.4 (td, 1H, $J = 5.76$ and 10.7), 2.6 (td, 1H, $J = 5.9$ and 10.9), 2.7 (m, 1H), 4.25 (d, 1H, $J = 9.7$), 7.2–7.5 (m, 5H).
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9. *N*2-(3,3-Dimethyl-butyl)-*N*1,*N*2-dimethyl-1-phenyl-propane-1,2-diamine **11** was prepared according to the procedure described in Ref. 8b: At 0 °C, MsCl (511 μl, 6.6 mmol) was added dropwise to a stirred solution of 2-[(3,3-dimethyl-butyl)-methyl-amino]-1-phenyl-propan-1-ol **9**, (1.37 g, 5.49 mmol) and dry Et_3N (1.3 ml, 9.3 mmol) in 27 ml of dry Et_2O. A white solid in suspension appeared. After 30 min, dry Et_3N (1.5 ml, 11 mmol) was added and the mixture was allowed to warm to room temperature. An 8 M solution of methylamine in ethanol (11.6 ml, 93.3 mmol) was then added and the mixture was stirred vigorously for 48 h at room temperature. Ethanol was evaporated, water and ether were added to the

mixture and the organic phase was separated. The aqueous phase was extracted with Et_2O three times and the combine organic phases were washed with a aqueous solution of 5% $NaHCO_3$, water, and finally dried over sodium sulfate and concentrated under vacuo to give 1.3 g of crude **11** (80%) as a yellow oil; ^1H NMR ($CDCl_3$, δ = ppm, J = Hz): $\delta = 0.6$ (d, 3H, $J = 6.6$), 0.9 (s, 9H), 1.35 (td, 1H, $J = 4.8$ and 12.6), 1.49 (td, 1H, $J = 5$ and 11.6), 2.25 (s, 3H), 2.3 (td, 1H, $J = 5.1$ and 11.6), 2.5 (td, 1H, $J = 5.3$ and 12.9), 2.75 (m, 1H), 3.2 (d, 1H, $J = 9.8$), 7.2–7.5 (m, 5H).

10. To a solution of *N*2-(3,3-dimethyl-butyl)-*N*1,*N*2-dimethyl-1-phenyl-propane-1,2-diamine **11** (800 mg, 2.64 mmol) in 375 μl of methanol were added 3-3-dimethylbutyraldehyde (524 μl, 3.97 mmol), sodium cyanoborohydride (330 mg, 5.29 mmol) and acetic acid (76 μl, 1.32 mmol). The mixture was stirred for 24 h, methanol was then evaporated and the residue diluted in ether. The organic layer was washed with a 10% NaOH aqueous solution. The product was purified by bulb-to-bulb distillation (155 °C, 0.4 mmHg), to yield 860 mg (94%) of (1*S*,2*S*)-*N*1,*N*2-bis(3,3-dimethylbuthyl)-*N*1,*N*2-dimethyl-1-phenylpropane-1,2-diamine,**12**, as a white solid. mp = 35 °C, $[\alpha]_D^{20} = +36.2$ (c 0.97, $CHCl_3$); 1H NMR ($CDCl_3$, δ = ppm, J = Hz): $\delta = 0.6$ (d, 3H, $J = 6.32$), 0.8 (s, 9H), 0.9 (s, 9H), 1.3–1.5 (m, 4H), 2.05 (m, 1H), 2.1 (s, 3H), 2.25 (s, 3H), 2.3 (m, 1H), 2.4–2.5 (m, 2H), 3.3 (m, 1H), 3.6 (d, 1H, $J = 10.4$), 7.1–7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, δ = ppm, J = Hz): $\delta = 10.4$, 29.9, 36.8, 38.2, 41.4, 42.1, 50.4, 56.1, 69.7, 127, 127.9, 129.7; IR (neat): 2953, 1465, 1362, 703; MS (m/z) 347 (M+1), 331, 277, 275, 232, 204, 156, 142, 118, 81, 43, 29; HRMS calcd for $C_{23}H_{43}N_2$ 347.3420, found 347.3404.